CHAPTER 1

INTRODUCTION

This chapter briefly describes the background of the Air Force Health Study (AFHS) and provides an overview of the study design, the morbidity component, and the purpose and format of this report. Additionally, this chapter provides considerations that should be made when interpreting the results provided in this report.

BACKGROUND

In January 1962, President John F. Kennedy approved a program of aerial herbicide dissemination for the purpose of defoliation and crop destruction, in support of tactical military operations in the Republic of Vietnam (RVN). This program, code-named Operation Ranch Hand, dispersed approximately 19 million gallons of herbicides on an estimated 10 to 20 percent of South Vietnam (1,2) from 1962 to 1971. Of the 19 million gallons dispersed, approximately 11 million gallons were "Agent Orange," the primary defoliant of the six herbicides used in the program.

From the start, Operation Ranch Hand was scrutinized intensely due to the controversial nature of the program and the political sensitivity to charges of chemical warfare contained in enemy propaganda. The concerns were initially based on military, political, and ecological issues, but shifted to issues of health in 1977. Numerous claims of exposure to herbicides, particularly Herbicide Orange and its dioxin contaminant, and subsequent perceived adverse health effects among U.S. military service personnel resulted in class action litigation and substantial controversy. Social concern for the Herbicide Orange issue continues to be manifest by continuing scientific research, media presentations, congressional hearings, and legal action.

The U.S. Air Force Medical Service's concern for the health of Air Force personnel exposed to herbicides was demonstrated in October 1978 when the Air Force Deputy Surgeon General made a commitment to Congress and the White House to conduct a health study on the Ranch Hand population, the aviators and ground support crews who disseminated the majority of the defoliants in the RVN. The prevailing reasons behind the study commitment included the availability of a population with a definitive occupational exposure to herbicides, a sufficient sample size for survey and clinical research, the ability to ascertain the population at risk, and an opportunity for the Air Force Medical Corps to fulfill its pledge to care for the Air Force community.

The U.S. Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas, was tasked by the Surgeon General to develop the Study Protocol. In 1982, after extensive peer review, the epidemiologic study began, and the Study Protocol was published (3). When the School of Aerospace Medicine was reorganized in 1990, the Armstrong Laboratory assumed responsibility for the AFHS.

Since 1978, numerous human studies of dioxin effects have been planned or initiated by governmental agencies, universities, and industrial firms. The key scientific issue in these studies was the extent of exposure (e.g., who was exposed and to what extent each individual was exposed). Unfortunately, in many of the human studies, population identification and exposure estimation, which are critical for a valid study, have often been scientifically elusive.

Studies of serum dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, or TCDD) levels have shown that of all the military personnel who served in the RVN, the Ranch Hand population was the most highly exposed to herbicides. In 1987, the Air Force initiated a collaborative study with the Centers for Disease Control (CDC) to measure the serum dioxin levels in the AFHS population. The results of that study clearly demonstrated that substantial elevated levels of dioxin could still be found in the serum of some Ranch Hands, as opposed to the absence of elevated levels of dioxin found in U.S. Army ground troops by the CDC (4,5). If dioxin should cause an adverse health effect, based on the principle of dose-response, the Ranch Hands should manifest more, or earlier evidence of adverse health.

STUDY DESIGN

The purpose of the study is to determine whether adverse health effects exist and can be attributed to occupational exposure to Herbicide Orange. The study, consisting of mortality and morbidity components, is based on a matched cohort design in a nonconcurrent prospective setting with followup studies. The nonconcurrent aspect of the design results from Ranch Hand exposure over time between 1962 and 1971. The interwoven study elements of multiple mortality assessments, a Baseline morbidity study, and five followup morbidity studies over 20 years provide a comprehensive approach to the detection of attributable adverse health effects. Complete details on the design are provided in the Study Protocol.

For the Baseline study, the population ascertainment process identified 1,264 Ranch Hand personnel who served in the RVN between 1962 and 1971. At the outset of the study, a Comparison group was identified consisting of veterans assigned to Air Force units operating C-130 cargo aircraft in Southeast Asia (SEA). Using a computerized selection procedure to identify Comparisons with similar characteristics to each Ranch Hand, a maximum of 10 Comparisons for each Ranch Hand was selected, matching on age, race, and military occupation. After personnel record reviews, each Ranch Hand determined to be eligible and fully suitable for study had an average of 8.2 matched Comparison subjects.

In the 1992 followup study, 952 of the 1,148 eligible Ranch Hands (83%) participated. Of the 1,195 eligible Original Comparisons, 912 (76%) participated, while 369 of the 567 replacement Comparisons (65%) invited to the 1992 followup chose to take part. Four Ranch Hands, 20 Original Comparisons, and 37 Replacement Comparisons participated for the first time at the 1992 followup examination. Complete information on the selection and participation of study participants can be found in Chapter 5 of this report, Study Selection and Participation.

The mortality component addresses mortality from the time of the RVN assignment. A Baseline mortality study was conducted in 1982, and the mortality followup consists of annual mortality updates for 20 years. For the Baseline mortality study and the first four updates, five individuals were randomly selected from the matched Comparison set for each Ranch Hand for a 1:5 design. Subsequent to 1987, the design was expanded to include all 19,080 veterans in the Comparison population.

MORBIDITY COMPONENT

The Baseline morbidity component, begun in 1982, reconstructed the medical history of each participant by reviewing and coding past medical records. A cross-sectional element, designed to assess the participant's current state of mental and physical health, was based on comprehensive questionnaires and physical examinations given to the participants. For this component of the study, each living Ranch Hand and the first living member of his Comparison set were selected to participate in the examination. The morbidity study followup comprises sequential questionnaires, medical record reviews, and physical examinations in 1985, 1987, 1992, 1997, and 2002.

The Baseline morbidity assessment, conducted in 1982, disclosed only minor differences between the Ranch Hands and Comparisons, and those differences were not traditional indicators of dioxin-related disease. The sustained commitment to pursue the Herbicide Orange question to its scientific conclusion was demonstrated by the conduct of the first two morbidity followups in 1985 and 1987. These followup examinations provided the opportunity to confirm or refute some of the Baseline findings and to explore subtle longitudinal changes. In the followup examinations, the mental and physical health status of the participants during the time interval since the Baseline study was assessed. The results of the followups showed a subtle but consistent narrowing of medical differences between the Ranch Hands and Comparisons since the Baseline study in 1982. There was not sufficient evidence to implicate a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.

For the Baseline and the 1985 and 1987 followup studies, the major focus of the analyses was to compare the health status of the Ranch Hands (i.e., the exposed cohort) with that of the Comparisons (i.e., the unexposed cohort). During the 1987 physical examination, the Air Force initiated a collaborative study with CDC to measure dioxin levels in the serum of Ranch Hands and Comparisons (4,6,7). The measurement of serum dioxin levels led to a thorough statistical evaluation to assess dose-response relationships between dioxin and approximately 300 health-related endpoints in 12 clinical areas. The statistical analyses associated with the serum data evaluated the association between a specified health endpoint and dioxin among the Ranch Hands, as well as contrasted the health of various categories of Ranch Hands having differing serum dioxin levels with the health of Comparisons having background levels of serum dioxin (8). The analysis of dose-response relationships based on serum assays provided an important enhancement from the previous AFHS investigations. This was the first large-scale study of dose-response effects based on an accurate measurement of current dioxin.

In 1992, the third followup was initiated. During a 2½-year period, data were collected, automated, and analyzed. As in 1985 and 1987, this followup study was conducted by Science Applications International Corporation (SAIC) in conjunction with Scripps Clinic and Research Foundation (SCRF), and National Opinion Research Center (NORC), working as a team with the Air Force. The analysis of data collected at the 1992 followup is the basis for this report.

PURPOSE OF THE REPORT

The subject of this report is the 1992 morbidity followup to the AFHS. The objective of the morbidity followup is to continue the investigation of the possible long-term health effects following exposure to TCDD. This report describes the procedures and results of the third morbidity followup of the AFHS.

This report is written primarily for clinical epidemiologists, clinicians, and biostatisticians so that they may fully evaluate the data and analytic techniques. Familiarity with the Study Protocol and prior mortality and morbidity reports is essential to a full understanding of this 20-year study. The report format has been established to be complete, rigorous, and straightforward on all issues so that maximum scientific credibility will be maintained. The intent of the background sections of the clinical chapters is to provide a broad overview of the literature with respect to dioxin endpoints. It is important to note that all statistical analyses in this report were prescribed by the Air Force and none are ad hoc analyses.

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ORGANIZATION OF THE REPORT

This report is organized as follows:

- Chapter 1 (Introduction) provides summary background information on the AFHS and discusses specific technical items and issues that may affect the different clinical area assessments.

- Chapter 2 (Dioxin Assay) describes the procedure used to draw blood for the serum dioxin measurements, the analytical method used to determine the dioxin level from the serum, and the quality control (QC) procedures associated with the serum dioxin data.

- Chapter 3 (Questionnaire Methodology) gives an overview of the development and implementation of the participant questionnaires.

- Chapter 4 (Physical Examination Methodology) describes the conduct and content of the physical examinations.

- Chapter 5 (Study Selection and Participation) presents the methods by which participants were selected and scheduled and also presents a discussion of the participant replacement strategy and the factors known or suspected to influence study participation. Sources of potential bias also are discussed.

- Chapter 6 (Quality Control) provides an overview of the specific quality assurance (QA) and QC measures developed and used throughout the 1992 followup.

- Chapter 7 (Statistical Methods) documents the statistical methods used in the individual clinical area assessments, and the statistical procedures and results of the half-life analyses performed by the Air Force.

- Chapter 8 (Covariate Associations with Estimates of Dioxin Exposure) examines the associations between exposure (Ranch Hand, Comparison, and measures of dioxin exposure) and the individual covariates used in the different clinical assessments.

- Chapters 9 through 20 present the results and medical discussions of the statistical analyses of the dependent variables for each clinical area. Each chapter also contains a brief overview of pertinent scientific literature. The 12 clinical chapters are as follows:

  - Chapter 9: General Health Assessment
  - Chapter 10: Neoplasia Assessment
  - Chapter 11: Neurological Assessment
  - Chapter 12: Psychological Assessment
  - Chapter 13: Gastrointestinal Assessment
  - Chapter 14: Dermatologic Assessment
  - Chapter 15: Cardiovascular Assessment
  - Chapter 16: Hematologic Assessment
  - Chapter 17: Renal Assessment
  - Chapter 18: Endocrine Assessment
  - Chapter 19: Immunologic Assessment
  - Chapter 20: Pulmonary Assessment

- Chapter 21 (Conclusions) summarizes the findings and medical discussions of the 12 clinical areas.

- Chapter 22 (Future Directions) summarizes the anticipated future activities and discusses possible modifications to the existing instruments and methodologies used to investigate the association between health status and dioxin exposure.

INTERPRETIVE CONSIDERATIONS

In the interpretation of results from any epidemiologic study, no single result should be evaluated in isolation or at face value, but rather in the context of the overall study design, the data collection procedures, the data analysis methods, and the approach to evaluating results. This especially applies to the AFHS. This effort is a large-scale, prospective

observational study in which thousands of measurements are generated on each participant, and those measurements and diagnoses are subjected to extensive statistical analyses entailing the testing of thousands of individual hypotheses. Each positive result should be scrutinized relative to other findings in this and other studies and relative to the statistical methods used and the medical and scientific plausibility of the results. Conversely, the lack of a positive result only denotes that the hypothesis of no association was not rejected. This has a very different conclusion than the assertion that there is no effect.

In this section, critical considerations in the evaluation of results from this study are reviewed. These considerations include study design and modeling considerations, information bias, consistency of results, strength of association, biological plausibility, interpretation of nonsignificant results, interpretation of graphics, extrapolation to other populations, and summarizing results. Other interpretive considerations, such as adjustments to analyses for covariates and interactions, multiple testing, trends in results within a clinical area, and power limitations, are discussed in greater statistical detail in Chapter 7, Statistical Methods.

Study Design and Modeling Considerations

Biased results will be produced if the assumptions underlying any of the statistical models are violated. Six models are used in this report to analyze the health effects of herbicide exposure in Vietnam. The first model contrasts the exposed population (Ranch Hands) with an unexposed group (Comparisons). The second model evaluates the relationship between estimated serum dioxin levels from the time of exposure (i.e., initial dioxin) with each health endpoint. The group contrast model is extended in the third model so that the Ranch Hand group is divided into three categories depending on current and estimated initial levels of serum dioxin, and each category is contrasted with the Comparison group. The final three models evaluate the associations between current serum dioxin levels and each health endpoint. The following current dioxin measurements are used in models four through six: lipid-adjusted current dioxin, whole-weight current dioxin, and whole-weight current dioxin with adjustment in the model for total lipids respectively. The parameters of these six models are summarized in Table 1-1.

As in any epidemiologic study, the group contrast (Ranch Hands versus Comparisons) is susceptible to bias toward the null hypothesis that both groups are equal, due to possible misclassification. It may not be true that all Ranch Hands and no Comparisons were occupationally exposed. Current dioxin data indicate that 40 percent of the Ranch Hands have background serum dioxin levels (10 ppt or less). These Ranch Hands either were never exposed or their initially elevated serum dioxin levels may have decayed to background levels during the time period between exposure and serum dioxin measurement. The AFHS has no additional data with which to determine whether or not Ranch Hands currently having background dioxin levels had elevated levels in the past.

The model analyzing the association of health endpoints with extrapolated initial dioxin levels also is vulnerable to bias, because it directly depends on two invalidated assumptions: (a) that dioxin elimination is by first-order pharmacokinetics, and (b) that all Ranch Hands have the same dioxin half-life (7.1 years). If dioxin elimination is first-order, but some

Table 1-1.
Parameters of Exposure Assessment Models

Model	Cohort(s)	Subset of Cohort	Exposure Characterized By:	Covariates in Analysis (not including endpoint-specific covariates)
1	Ranch Hands and Comparisons	All participants	Group (Ranch Hands versus Comparisons and military occupation	--
2	Ranch Hands	Lipid-adjusted current dioxin measurement >10 ppt	Extrapolated initial dioxin	PBF at time of duty and PBF change
3	Ranch Hands and Comparisons	RH: Current dioxin measurement C: Lipid-adjusted current dioxin measurement ≤ 10 ppt	Group (Ranch Hands versus Comparisons); Ranch Hands categorized according to current and estimated initial dioxin levels	PBF at time of duty and PBF change
4	Ranch Hands	Current dioxin measurement	Lipid-adjusted current dioxin: (102.6*whole-weight current dioxin/total lipids)	--
5	Ranch Hands	Current dioxin measurement	Whole-weight current dioxin	--
6	Ranch Hands	Current dioxin measurement	Whole-weight current dioxin	Total lipids

Note: RH = Ranch Hands.
C = Comparisons.
"PBF at time of duty" = Percent body fat at the time of duty in SEA.
"PBF change" = Change in percent body fat from the time of duty in SEA to the date of dioxin draw.

Ranch Hands have a shorter half-life than others, then there would have been misclassification of initial dioxin exposure. If the clinical endpoint is not associated with a factor that affects the elimination rate (e.g., relative weight change), then estimates of the relative risk for common diseases associated with low and high levels of initial dioxin, in general, will be biased toward unity. However, if the clinical endpoint is associated with a factor that affects the elimination rate, then the relative risk will be biased away from unity.

The half-life of dioxin has been found to change significantly with percent body fat and age in the 337 Ranch Hands having paired dioxin measurements above 10 ppt; one derived from serum drawn in 1982 and the other from serum drawn in 1987 (9). Half-life increased significantly with higher levels of obesity and decreased significantly with weight gain and age. The constant 7.1 year half-life used in this report was derived from an earlier half-life study based on 36 subjects (6). The longer half-life estimate derived from 337 subjects was developed 3 years after the statistical plan for this report, too late for application to these data, because the statistical analyses summarized in this report had already begun. As a partial solution to the observed relationship of half-life to obesity and weight gain, analyses using estimated initial dioxin levels were adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin (see Chapter 7, Statistical Methods).

The validity of the constant half-life assumption cannot be assessed until the half-life study is expanded to include dioxin measurements taken in 1992, giving three repeated dioxin measures for each of the Ranch Hands in the half-life study. These analyses are expected to be published in 1995. Dioxin measurements on multiple blood specimens taken from 20 males exposed during a factory explosion near Seveso, Italy (10), will be evaluated to further assess the first-order elimination assumption.

In order to account for the possible misclassification of exposure between groups, the third statistical model categorizes Ranch Hands into three levels of exposure: background levels of current dioxin, low levels of estimated initial dioxin, and high levels of estimated initial dioxin. Each Ranch Hand dioxin category is contrasted with Comparisons having background levels of current dioxin. Although this model is less dependent upon the accuracy of the initial dioxin estimation procedure than the model using continuous initial dioxin estimates, the classification of the Ranch Hands is subject to bias if the half-life and first-order dioxin elimination assumptions are not valid. Also, the Ranch Hands with background levels of current serum dioxin (10 ppt or less) may contain both unexposed Ranch Hands and exposed Ranch Hands whose serum dioxin levels have decayed to background levels. This will result in a bias towards the null hypothesis of no dioxin effect on the health endpoint.

In the analyses of this model in this report and in the Serum Dioxin Analysis of the 1987 Followup, a "checkmark pattern" has become prevalent. The checkmark pattern is defined as the occurrence of a lower percentage of abnormalities in the Ranch Hands with background dioxin levels than in background Comparisons, but a greater percentage of abnormalities in Ranch Hands with high levels of serum dioxin than in the Comparisons. A checkmark pattern is expected when there is a positive association between disease and dioxin in Ranch Hands and the prevalence of disease in the two groups is nearly equal. This

circumstance could arise if there is a large degree of misclassification between the exposure groups (Ranch Hands and Comparisons) with regard to dioxin levels that conceal the difference between exposed and unexposed participants (11) (as may be the case with 40% of the Ranch Hands having background levels). As a corollary, the pattern is expected if body fat, but not dioxin, is associated with disease in Ranch Hands and the prevalence of disease in the two exposure groups is nearly equal. This circumstance could arise if there is a large degree of similarity between the two groups with regard to body fat (as is the case because the group means on body fat are nearly equal). A second corollary is that the checkmark pattern is expected when disease is associated with both dioxin and body fat in Ranch Hands and the prevalence of disease in the two groups is nearly equal. This last circumstance could arise if there is a large degree of similarity between the two groups with regard to body fat and dioxin (as is the case for the reasons described above).

The three models that analyze associations between current serum dioxin and health endpoints are less subject to bias than the previous models. However, current serum dioxin levels may not be good measures of exposure if serum dioxin elimination rates differ among individuals. Current serum dioxin levels also were extrapolated from 1992 measurements to 1987 for participants without current serum dioxin levels measured in 1987. Therefore, these current dioxin measurements are subject to the potential bias from the half-life and first-order elimination assumptions that also affect the initial dioxin estimates.

Information Bias

Information bias, represented by the over-reporting of disease symptoms, was minimized by verifying all diseases and conditions with medical records. It is possible that conditions in Ranch Hands may be more verifiable because they may have been seen by physicians more often than Comparisons; this would be revealed by group differences in the quantity and content of medical records. Because there is no way to quantify these aspects, this potential source of bias remains unexplored. This bias, however, if it exists, would affect only estimates of health effects used in the models contrasting Ranch Hands and Comparisons because Comparison data were not used in models assessing associations between health effects and dioxin. Information bias due to errors in the data introduced through data entry or machine error is negligible. All laboratory results were subject to strict QC procedures, historical data were verified completely by medical record review, and medical data were subjected to strict QC standards (Chapter 6, Quality Control).

Consistency of Results

Adverse health effects in Ranch Hands attributable to herbicide or dioxin should be confirmed by internally and externally consistent findings. An internally consistent finding does not contradict other findings in the report, and an externally consistent finding has been previously established by other research. All statistically significant findings in this report were subjected to clinical review and were compared to published results from other research to identify consistent findings.

Strength of Association

Ideally, an adverse effect, if it exists, would be revealed by a strong association between categorized dioxin and a disease condition; that is, by a statistically significant relative risk greater than 2.0 for Ranch Hands with high categorized dioxin levels relative to the Comparisons (12). Statistically significant relative risks less than 2.0 are generally considered to be less important than larger risks because relative risks less than 2.0 can easily arise due to unrecognized bias or confounding. Relative risks greater than 5.0 are less subject to this concern. The numbers 2.0 and 5.0 are epidemiologic guidelines regarding analyses of association between a dichotomous endpoint (disease, no disease) and exposure (yes, no). No such general guidelines have been formulated regarding the analysis of continuously distributed endpoints (such as cholesterol) versus continuously distributed exposure (such as initial or current serum dioxin measurements).

Biological Plausibility

The assessment of biological plausibility requires consideration of the feasibility, in biological terms, of the exposure under study to produce the effect of interest. While a lack of biological credibility or even a contradiction of biological knowledge can lead to the dismissal of a significant result, the failure to perceive a mechanism may reflect only ignorance of the state of nature. On the other hand, it is easy to hypothesize biological mechanisms that relate almost any exposure to almost any disease. Thus, while important, the biological explanation of results must be interpreted with caution. In the AFHS, statistically significant results are subjected to medical review and confirmation from previously published results in order to identify consistent and biologically plausible results.

Interpretation of Nonsignificant Results

In this study, a lack of significant results relating dioxin to a particular disease only means that the study is unable to detect a relationship between dioxin and health. This does not imply that a relationship may not exist, but that, if it does exist, it was not detected. A lack of significant results does not mean that dioxin is safe or that there is no relationship between dioxin and health. The AFHS was not designed to establish safety. Rather, this study was designed to determine whether a hazard existed for the exposed personnel. Determination of safety would require a study at least 10 times as large, as determined in a 1985 study presenting minimal sample-size criteria for proof of safety and hazard in studies of environmental and occupational exposures (13).

Graphics

Scatterplots of selected continuous health endpoints were included as aids to interpretation. The graphics alone are not sufficient to assess the relationship between dioxin and health. For example, a trend may be seen in a plot, but it could be statistically nonsignificant because the number of abnormalities is small. On the other hand, a statistically significant result can be clarified by the graphics, especially if the result depends on a few data points that appear far from the main cluster.

Extrapolation to Armed Forces Ground Troops

Extrapolation of the serum dioxin results to the general population of ground troops who served in Vietnam is difficult because Ranch Hand and ground troop exposure situations were very different. Based on serum dioxin testing results done by CDC (7) and others (14), nearly all ground troops tested have current levels of dioxin similar to background levels. Even combat troops who served in herbicide-sprayed areas of Vietnam had current levels indistinguishable from levels in men who never left the United States (with mean dioxin levels of 4.2 ppt and 4.1 ppt respectively). The AFHS subgroup most like the ground troops in terms of current dioxin levels are Ranch Hands who currently have background levels of dioxin (10 ppt or less). Therefore, if the results of the AFHS are applied to the general population of Vietnam veterans, the focus should be on the "Background" Ranch Hand versus Comparison contrast. However, extrapolating the results of these analyses to Vietnam veterans still should be made cautiously. There may be demographic distinctions between the "Background" group of Ranch Hands and other Vietnam veterans that may be related to health. Also, if Ranch Hands with background levels of current serum dioxin showed a significant health detriment relative to Comparisons, but there was no significant detriment for Ranch Hands with high serum dioxin levels, the biological plausibility of such an effect would be questionable, because this would not indicate a dose-response effect. In general, the analyses in this report found that Ranch Hands with background levels of current serum dioxin did not show a significant health detriment relative to Comparisons. This was particularly true for the analyses that exhibited a statistically significant health detriment in Ranch Hands with high levels of current serum dioxin.

Summary of Results

A study of this scope with a multitude of endpoints demands, and at the same time defies, meaningful summary tabulation. Such summaries can be misleading because they ignore correlations between the endpoints, correlations between study-cycle results, and the nonquantifiable medical importance of each endpoint. In fact, many endpoints are redundant (e.g., psychological scales and indices developed from combining multiple variables). In addition, such tabulations combine endpoints that are not comparable. For example, diminished sense of smell is of less medical importance than the presence of a malignant neoplasm. Nevertheless, the AFHS presents a summary of all statistical results (see Appendix Q-1). However, these summaries can be misleading and must be interpreted carefully—an elementary tally of significant, or nonsignificant, results is not appropriate.

CHAPTER 1
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